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Request for grant of a patent

1/77

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1.	Your reference	TSJ/SVH/44552GB1
2.	Patent application number	15 SEP 2003 0321607.4
3.	Full name, address and post code of the or each applicant	Vectura Ltd 1 Prospect West Wiltshire Chippenham SN14 6FH
	Patents ADP number	8610727001
	If the applicant is a corporate body, give the country/state of its incorporation	United Kingdom
4.	Title of the invention	Manufacture of Pharmaceutical Compositions
5.	Name of your agent	VENNER, SHIPLEY & CO
	"Address for service" in the United Kingdom to which all correspondence should be sent	20 LITTLE BRITAIN LONDON EC1A 7DH
	Patents ADP	1669004

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Date
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12. Name and daytime telephone number of person to contact in the United Kingdom

Timothy J S Jump
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Manufacture of Pharmaceutical Compositions

The present invention relates to particles and to methods of making particles. In particular, the invention relates to methods of making composite active particles comprising a pharmaceutically active material for pulmonary inhalation, the method comprising a jet milling process.

It is known to administer pharmaceutically active agents to a patient in the form of fine, dry particles (active particles), for example, by pulmonary administration of a particulate medicament composition which is inhaled by the patient. Pulmonary administration is particularly suitable for medicaments which are intended to cure or alleviate respiratory conditions such as asthma and for medicaments which are not suitable for oral ingestion, such as certain biological macromolecules, for example insulin. Known devices for the administration of drugs to the respiratory system include pressurised metered dose inhalers (pMDIs) and dry powder inhalers (DPIs).

The size of the active particles is of great importance in determining the site of the absorption in the lung. In order for the particles be carried deep into the lungs, the particles must be very fine, for example having a mass median aerodynamic diameter (MMAD) of less than 10μm. Particles having aerodynamic diameters greater than 10μm are likely to impact the walls of the throat and generally do not reach the lung. Particles having aerodynamic diameters in the range of 5μm to 2μm will generally be deposited in the respiratory bronchioles whereas smaller particles having aerodynamic diameters in the range of 3 to 0.05μm are likely to be deposited in the alveoli.

Particles having a diameter of less than 10μm are, however, thermodynamically unstable due to their high surface area to volume ratio, which provides significant excess surface free energy and encourages particles to agglomerate. In the inhaler, agglomeration of small particles and adherence of particles to the walls of the inhaler are problems that result in the active particles leaving the inhaler as large agglomerates or being unable to leave the inhaler and remaining adhered to the interior of the device, or even clogging or blocking the inhaler.

The uncertainty as to the extent of formation of stable agglomerates of the particles between each actuation of the inhaler, and also between different inhalers and different batches of particles, leads to poor dose reproducibility. Furthermore, the formation of agglomerates means that the MMAD of the active particles can be vastly increased, with agglomerates of the active particles not reaching the required part of the lung.

The metered dose (MD) of a dry powder formulation is the total mass of active agent present in the metered form presented by the inhaler device in question. For example, the MD might be the mass of active agent present in a capsule for a Cyclohaler (trade mark), or in a foil blister in an Aspirair (trade mark) device.

The emitted dose (ED) is the total mass of the active agent emitted from the device following actuation. It does not include the material left inside or on the surfaces of the device. The ED is measured by collecting the total emitted mass from the device in an apparatus frequently referred to as a dose uniformity sampling apparatus (DUSA), and recovering this by a validated quantitative wet chemical assay.

The fine particle dose (FPD) is the total mass of active agent which is emitted from the device following actuation which is present in an aerodynamic particle size smaller than a defined limit. This limit is generally taken to be 5μm if not expressly stated to be an alternative limit, such as 3μm or 1μm, etc. The FPD is measured using an impactor or impinger, such as a twin stage impinger (TSI), multi-stage impinger (MSI), Andersen Cascade Impactor or a Next Generation Impactor (NGI). Each impactor or impinger has a pre-determined aerodynamic particle size collection cut points for each stage. The FPD value is obtained by interpretation of the stage-by-stage active agent recovery quantified by a validated quantitative wet chemical assay where either a simple stage cut is used to determine FPD or a more complex mathematical interpolation of the stage-by-stage deposition is used.

The fine particle fraction (FPF) is normally defined as the FPD divided by the ED and expressed as a percentage. Herein, the FPF of ED is referred to as FPF(ED) and is calculated as FPF(ED) = (FPD/ED) x 100%.

The fine particle fraction (FPF) may also be defined as the FPD divided by the MD and expressed as a percentage. Herein, the FPF of MD is referred to as FPF(MD), and is calculated as FPF(MD) = (FPD/MD) x 100%.

The tendency of fine particles to agglomerate means that the FPF of a given dose is highly unpredictable and a variable proportion of the fine particles will be administered to the lung, or to the correct part of the lung, as a result.

In an attempt to improve this situation and to provide a consistent FPF and FPD, dry powder formulations often include additive material.

The additive material is intended to reduce the cohesion between particles in the dry powder formulation. It is thought that the additive material interferes with the weak bonding forces between the small particles, helping to keep the particles separated and reducing the adhesion of such particles to one another, to other particles in the formulation if present and to the internal surfaces of the inhaler device. Where agglomerates of particles are formed, the addition of particles of additive material decreases the stability of those agglomerates so that they are more likely to break up in the turbulent air stream created on actuation of the inhaler device, whereupon the particles are expelled from the device and inhaled. As the agglomerates break up, the active particles return to the form of small individual particles which are capable of reaching the lower lung.

In the prior art, dry powder formulations are discussed which include distinct particles of additive material (generally of a size comparable to that of the fine active particles). In some embodiments, the additive material may form a coating, generally a discontinuous coating, on the active particles and/or on any carrier particles.

Preferably, the additive material is an anti-adherent material and it will tend to reduce the cohesion between particles and will also prevent fine particles becoming attached to the inner surfaces of the inhaler device. Advantageously, the additive material is an anti-friction agent or glidant and will give the powder formulation better flow properties in the inhaler. The additive materials used in this way may not necessarily be usually referred to as anti-adherents or anti-friction agents, but they will have the effect of decreasing the cohesion between the particles or improving the flow of the powder. The additive materials are sometimes referred to as force control agents (FCAs) and they usually lead to better dose reproducibility and higher FPFs.

Therefore, an additive material or FCA, as used herein, is a material whose presence on the surface of a particle can modify the adhesive and cohesive surface forces experienced by that particle, in the presence of other particles. In general, its function is to reduce both the adhesive and cohesive forces.

The reduced tendency of the particles to bond strongly, either to each other or to the device itself, not only reduces powder cohesion and adhesion, but can also promote better flow characteristics. This leads to improvements in the dose reproducibility because it reduces the variation in the amount of powder metered out for each dose and improves the release of the powder from the device. It also increases the likelihood that the active material, which does leave the device, will reach the lower lung of the patient.

It is favourable for unstable agglomerates of particles to be present in the powder when it is in the inhaler device. As indicated above, for a powder to leave an inhaler device efficiently and reproducibly, the particles of such a powder should be large, preferably larger than 40μm. Such a powder may be in the form of either individual particles having a size of 40μm or larger and/or agglomerates of finer particles, the agglomerates having a size of 40μm or larger. The agglomerates formed can have a size of as much as 100μm and, with the addition of the additive material, those agglomerates are more likely to be broken down efficiently in the turbulent airstream created on inhalation. Therefore, the formation of unstable agglomerates

of particles in the powder may be favoured compared with a powder in which there is substantially no agglomeration.

The reduction in the cohesion and adhesion between the active particles can lead to equivalent performance with reduced agglomerate size, or even with individual particles.

The terms "additive particles" and "particles of additive material" are used interchangeably herein. The additive particles comprise one or more additive materials (or FCA). Preferably, the additive particles consist essentially of the additive material or FCA.

Known additive materials usually consist of physiologically acceptable material, although the additive material may not always reach the lung. For example, where the additive particles are attached to the surface of carrier particles, they will generally be deposited, along with those carrier particles, at the back of the throat of the user.

Advantageously, the additive material includes one or more compounds selected from amino acids and derivatives thereof, and peptides and derivatives thereof. Amino acids, peptides and derivatives of peptides are physiologically acceptable and give acceptable release of the active particles on inhalation.

It is particularly advantageous for the additive material to comprise an amino acid. The additive material may comprise one or more of any of the following amino acids: leucine, isoleucine, lysine, valine, methionine, and phenylalanine. The additive may be a salt or a derivative of an amino acid, for example aspartame or acesulfame K. Preferably, the additive particles consist substantially of an amino acid, more preferably of leucine, advantageously L-leucine. The D-and DL-forms may also be used. As indicated above, leucine has been found to give particularly efficient dispersal of the active particles on inhalation.

The additive material may include one or more water soluble substances. This helps absorption of the substance by the body if the additive reaches the lower lung. The additive material may include dipolar ions, which may be zwitterions.

Alternatively, the additive material may comprise a phospholipid or a derivative thereof. Lecithin has been found to be a good material for the additive material.

The additive material may comprise a metal stearate, or a derivative thereof, for example, sodium stearyl fumarate or sodium stearyl lactylate. Advantageously, the additive material comprises a metal stearate. For example, zinc stearate, magnesium stearate, calcium stearate, sodium stearate or lithium stearate. Preferably, the additive material comprises magnesium stearate.

The additive material may include or consist of one or more surface active materials, in particular materials that are surface active in the solid state, which may be water soluble, for example lecithin, in particular soya lecithin, or substantially water insoluble, for example solid state fatty acids such as oleic acid, lauric acid, palmitic acid, stearic acid, erucic acid, behenic acid, or derivatives (such as esters and salts) thereof such as glyceryl behenate. Specific examples of such materials are: phosphatidylcholines, phosphatidylethanolamines, phosphatidylglycerols and other examples of natural and synthetic lung surfactants; lauric acid and its salts, for example, sodium lauryl sulphate, magnesium lauryl sulphate; triglycerides such as Dynsan 118 and Cutina HR; and sugar esters in general. Alternatively, the additive may be cholesterol.

Other possible additive materials include sodium benzoate, hydrogenated oils which are solid at room temperature, talc, titanium dioxide, aluminium dioxide, silicon dioxide and starch.

In general, the optimum amount of additive material to be included in a dry powder formulation will depend on the chemical composition and other properties of the additive material and of the active material, as well as upon the nature of other

particles, such as carrier particles, if present. In general, the efficacy of the additive material is measured in terms of the FPF of the composition.

In a further attempt to improve extraction of the dry powder from the dispensing device and to provide a consistent FPF and FPD, dry powder formulations often include coarse carrier particles of excipient material mixed with fine particles of active material. Rather than sticking to one another, the fine active particles tend to adhere to the surfaces of the coarse carrier particles whilst in the inhaler device, but are supposed to release and become dispersed upon actuation of the dispensing device and inhalation into the respiratory tract, to give a fine suspension. The carrier particles preferably have MMADs greater than 90μm.

The inclusion of coarse carrier particles is also very attractive where very small doses of active agent are dispensed. It is very difficult to accurately and reproducibly dispense very small quantities of powder and small variations in the amount of powder dispensed will mean large variations in the dose of active agent where the powder comprises mainly active particles. Therefore, the addition of a diluent, in the form of large excipient particles will make dosing more reproducible and accurate.

Carrier particles may be of any acceptable excipient material or combination of materials. For example, the carrier particles may be composed of one or more materials selected from sugar alcohols, polyols and crystalline sugars. Other suitable carriers include inorganic salts such as sodium chloride and calcium carbonate, organic salts such as sodium lactate and other organic compounds such as polysaccharides and oligosaccharides. Advantageously, the carrier particles comprise a polyol. In particular, the carrier particles may be particles of crystalline sugar, for example mannitol, dextrose or lactose. Preferably, the carrier particles are composed of lactose.

Advantageously, substantially all (by weight) of the carrier particles have a diameter which lies between 20μm and 1000μm, more preferably 50μm and 1000μm.

Preferably, the diameter of substantially all (by weight) of the carrier particles is less than 355μm and lies between 20μm and 250μm.

Preferably at least 90% by weight of the carrier particles have a diameter between from 60μm to 180μm. The relatively large diameter of the carrier particles improves the opportunity for other, smaller particles to become attached to the surfaces of the carrier particles and provides good flow and entrainment characteristics and improved release of the active particles in the airways to increase deposition of the active particles in the lung.

The ratios in which the carrier particles (if present) and composite active particles are mixed will, of course, depend on the type of inhaler device used, the type of active particles used and the required dose. The carrier particles may be present in an amount of at least 50%, more preferably 70%, more preferably 80%, advantageously 90% and most preferably 95%, based on the combined weight of the composite active particles and the carrier particles.

However, a further difficulty is encountered when adding coarse carrier particles to a composition of fine active particles and that difficulty is ensuring that the fine particles detach from the surface of the large particles upon actuation of the delivery device.

The step of dispersing the active particles from other active particles and from carrier particles, if present, to form an aerosol of fine active particles for inhalation is significant in determining the proportion of the dose of active material which reaches the desired site of absorption in the lungs. In order to improve the efficiency of that dispersal it is known to include in the composition additive materials of the nature discussed above. Compositions comprising fine active particles and additive materials are disclosed in WO 97/03649 and WO 96/23485.

In light of the foregoing problems associated with known dry powder formulations, even when including additive material and/or carrier particles, it is an aim of the present invention to provide dry powder compositions which have physical and

chemical properties which lead to an enhanced FPF and FPD. This leads to greater dosing efficiency, with a greater proportion of the dispensed active agent reaching the desired part of the lung for achieving the required therapeutic effect.

In particular, the present invention seeks to optimise the preparation of particles of active agent used in the dry powder composition by engineering the particles making up the dry powder composition and, in particular, by engineering the particles of active agent. It is proposed to do this by adjusting and adapting the milling process used to form the particles of active agent.

The word "milling" as used herein refers to any mechanical process which applies sufficient force to the particles of active material that it is capable of breaking coarse particles (for example, particles with a MMAD greater than 100μm) down to fine particles (for example, having a MMAD not more than 50μm) or which applies a relatively controlled compressive force.

Fine particles of active material suitable for pulmonary administration have often been prepared by milling in the past. However, when using many of the known milling techniques, once the particles reach a minimum size, referred to as the "critical size", they tend to re-combine at the same rate as being fractured, or do not fracture effectively and therefore no further reduction in the particle size is achieved. Critical sizes are specific to particular mills and sets of milling conditions.

Thus, manufacture of fine particles by milling can require much effort and there are factors which consequently place limits on the minimum size of particles of active material which can be achieved, in practice, by such milling processes.

Improvements have been made to conventional milling methods by co-milling active material with additive materials. Such "co-milling" is described in WO 02/43701. This earlier patent application describes methods for making composite active particles for use in a pharmaceutical composition for pulmonary administration using a milling step. In these improved methods, particles of active material are milled in the presence of particles of an additive material which is

suitable for the promotion of the dispersal of the composite active particles upon actuation of an inhaler. This application is directed to methods of compressive milling, such as Mechano-Fusion and ball milling, or to impact milling in a non-compressible fluid, such as a high pressure homogeniser.

The resultant composite active particles are fine particles of active material which have, upon their surfaces, an amount of the additive material. The additive material is preferably in the form of a coating on the surfaces of the particles of active material. The coating may be a discontinuous coating. The additive material may be in the form of particles adhering to the surfaces of the particles of active material.

At least some of the composite active particles may be in the form of agglomerates. However, when the composite active particles are included in a pharmaceutical composition, the additive material promotes the dispersal of the composite active particles on administration of that composition to a patient, via actuation of an inhaler.

"Actuation of an inhaler" refers to the process during which a dose of the powder is removed from its rest position in the inhaler. That step takes place after the powder has been loaded into the inhaler ready for use. The effectiveness of that promotion of dispersal has been found to be enhanced in comparison to a composition made by simple blending of similarly sized particles of active material with additive material.

In the prior art, it is stated that milling can be used to substantially decrease the size of particles of active agent. However, if the particles of active agent are already fine, for example have a MMAD of less than 20μm prior to the milling step, the size of those particles may not be significantly reduced where the milling of these active particles takes place in the presence of an additive material. Rather, milling of fine active particles with additive particles using the methods described in the prior art (for example, in WO 02/43701) will result in the additive material becoming deformed and being smeared over or fused to the surfaces of the active particles. The resultant composite active particles have been found to be less cohesive after

the milling treatment. However, there is still the disadvantage that this is not combined with a significant reduction in the size of the particles.

The co-milling processes described in the prior art favour the use of the milling processes known as the Mechano-Fusion and Cyclomix methods. These processes were found to apply a high enough degree of force to separate the individual particles of active material and to break up tightly bound agglomerates of the active particles such that effective mixing and effective application of the additive material to the surfaces of those particles is achieved. An especially desirable aspect of the described co-milling processes was that the additive material becomes deformed in the milling and may be smeared over or fused to the surfaces of the active particles.

The milling steps used in the prior art co-milling generally involve bringing the additive particles into close contact with the surfaces of the active particles. In order to achieve coated particles, a degree of intensive mixing is required to ensure a sufficient break-up of agglomerates of both constituents, dispersal and even distribution of additive over the active particles. The process uses shear to mix the constituents and to break up their constituent agglomerates, and then compressive force to smear the additive and mechanically fuse it to the host surface.

A wide range of milling devices and conditions are said to be suitable to achieve the desired results discussed above. The milling conditions, for example, intensity of milling and duration, should be selected to provide the required degree of force.

Ball milling is a suitable milling method. Centrifugal and planetary ball milling are especially preferred methods. Alternatively, a high pressure homogeniser may be used in which a fluid containing the particles is forced through a valve at high pressure producing conditions of high shear and turbulence. Such homogenisers may be more suitable than ball mills for use in large scale preparations of the composite active particles.

Suitable homogensiers include EmulsiFlex high pressure homogenisers which are capable of pressures up to 4000 bar, Niro Soavi high pressure homogenisers

(capable of pressures up to 2000 bar), and Microfluidics Microfluidisers (maximum pressure 2750 bar). The milling step may, alternatively, involve a high energy media mill or an agitator bead mill, for example, the Netzsch high energy media mill, or the DYNO-mill (Willy A. Bachofen AG, Switzerland). Alternatively the milling may be a dry coating high energy process such as a Mechano-Fusion system (Hosokawa Micron Ltd) or a Hybridizer (Nara).

Especially preferred prior art co-milling methods are those involving the Mechano-Fusion, Hybridiser and Cyclomix instruments. Indeed, the milling step is said to preferably involve the compression of the mixture of active and additive particles in a gap (or nip) of fixed, predetermined width, for example as in the Mechano-Fusion and Cyclomix methods.

In light of the foregoing, it is an aim of the present invention to achieve a further reduction in particle size whilst co-milling active and additive particles to produce composite active particles. In particular, it is an aim of the present invention to provide composite active particles having an enhanced FPD and FPF, compared to those disclosed in the prior art.

According to a first aspect of the present invention, a method is provided for making composite active particles for use in a pharmaceutical composition for pulmonary inhalation, the method comprising jet milling active particles in the presence of particles of additive material, preferably wherein the jet milling is conducted using air or a compressible gas or fluid.

The additive materials used in this co-jet milling process can be any of the additive materials discussed herein.

In one embodiment, the jet milling is carried out at an inlet pressure of between 0.1 and 3 bar, to achieve blending of the active and additive particles.

In an alternative embodiment, the jet milling is carried out at an inlet pressure of between 3 and 12 bar, to achieve a reduction of the sizes of the active and additive particles.

In a preferred embodiment of the invention, the additive particles comprise an amino acid, a metal stearate or a phospholipid. More preferably, the additive particles comprise one or more of L-, D- or DL- forms of leucine, isoleucine, lysine, valine, methionine, phenylalanine, or Aerocine, lecithin or magnesium stearate. In one embodiment, the additive particles comprise leucine and preferably l-leucine.

In another embodiment, 90% by mass of the active particles jet-milled are initially less than 20μm in diameter. More preferably, 90% by mass of the active particles jet-milled are initially less than 10μm in diameter, and most preferably less than 5μm in diameter.

In another embodiment, 90% by mass of the additive particles jet-milled are initially less than 20μm in diameter. More preferably, 90% by mass of the additive particles jet-milled are initially less than 10μm in diameter, and most preferably less than 5μm in diameter or less than 3μm in diameter

In another embodiment, the jet milling is carried out at temperatures below room temperature, preferably at a temperature below 10°C, more preferably at a temperature below 0°C.

In accordance with a second aspect of the present invention, a pharmaceutical dry powder composition for pulmonary inhalation is provided, comprising composite active particles made by a method according to the first aspect of the invention.

The MMAD of the composite active particles is preferably not more than 10μm, and advantageously it is not more than 5μm, more preferably not more than 3μm, even more preferably not more than 2μm, more preferably not more than 1.5μm, even more preferably not more than 1.2 μm and most preferably not more than 1μm.

Accordingly, advantageously at least 90% by weight of the composite active particles have a diameter of not more than 10μm, advantageously not more than 5μm, preferably not more than 3μm, even more preferably not more than 2.5μm, even more preferably not more than 2μm and more preferably not more than 1μm.

In a preferred embodiment of the present invention the resultant dry powder formulation has a reproducible FPF(ED) of at least 70%. Preferably, the FPF(ED) will be at least 80%, more preferably the FPF(ED) will be at least 85%, and most preferably the FPF(ED) will be at least 90%.

In a further preferred embodiment, the dry powder formulation has a reproducible FPF(MD) of at least 60%. Preferably, the FPF(MD) will be at least 70%, more preferably the FPF(MD) will be at least 80%, and most preferably the FPF(MD) will be at least 85%.

Jet mills are capable of reducing solids to particle sizes in the low-micron to submicron range. The grinding energy is created by gas streams from horizontal grinding air nozzles. Particles in the fluidized bed created by the gas streams are accelerated towards the centre of the mill, colliding with slower moving particles. The gas streams and the particles carried in them create a violent turbulence and as the particles collide with one another they are pulverized.

In the past, jet-milling would not have been considered attractive for co-milling active and additive particles, with processes like Mechano-Fusion and Cyclomixing being clearly preferred. The collisions between the particles in a jet mill are somewhat uncontrolled and those skilled in the art, therefore, would have considered it unlikely for this technique to be able to provide the desired deposition of a coating of additive material on the surface of the active particles. Moreover, it was believed that, unlike the situation with Mechano-Fusion and Cyclomixing, segregation of the powder constituents occurred in jet mills, such that the finer particles, that were believed to be the most effective, could escape from the process. In contrast, it could be clearly envisaged how techniques such as Mechano-Fusion would result in such coating.

As the name suggests, Mechano-Fusion is a dry coating process designed to mechanically fuse a first material onto a second material. The first material is generally smaller and/or softer than the second. The Mechano-Fusion and Cyclomix working principles are distinct from alternative milling techniques in having a particular interaction between an inner element and a vessel wall, and are based on providing energy by a controlled and substantial compressive force.

The fine active particles and the additive particles are fed into the Mechano-Fusion driven vessel, where they are subject to a centrifugal force and are pressed against the vessel inner wall. The powder is compressed between the fixed clearance of the drum wall and a curved inner element with high relative speed between drum and element. The inner wall and the curved element together form a gap or nip in which the particles are pressed together. As a result, the particles experience very high shear forces and very strong compressive stresses as they are trapped between the inner drum wall and the inner element (which has a greater curvature than the inner drum wall). The particles are pressed against each other with enough energy to locally heat and soften, break, distort, flatten and wrap the additive particles around the core particle to form a coating. The energy is generally sufficient to break up agglomerates and some degree of size reduction of both components may occur.

As illustrated by the experimental results set out below, it has been surprisingly found that co-milling active particles with additive particles using jet milling results in composite active particles having significantly better FPF and FPD than those produced by co-milling using Mechano-Fusion.

A number of formulation approaches were examined. As Mechano-Fusion of drug particles had been shown in the prior art to significantly reduce cohesion, this was further tested. The aim was to Mechano-Fuse active particles with additive particles in order to significantly reduce powder cohesion and adhesion, and to allow resuspension and dispersion to occur in both high energy active and lower energy passive devices.

Jet milling has previously been shown to be capable of significantly reducing the median primary particle size of active particles (for example, from 3 or 2μm to 1μm), while also allowing good aerosolisation from a delivery device. This further reduction in primary particle size is considered to be advantageous for delivery of systemically targeted molecules to the deep lung. The aim was to co-jet mill active particles with additive particles in order to reduce primary particle size while still achieving a reduction in the level of powder cohesion and adhesion. This was tested at high and low air pressures.

Test Methods

All materials were evaluated in the Next Generation Impactor (NGI). Details of the test are provided in each case.

In addition, some of the resulting powders were characterised by a standard dispersion test. This process required feeding approximately 20mg of test powder into the Malvern Mastersizer via a modified Sirocco powder feeder. The powder was challenged with 4 dispersion energies, provided by 4 air pressure variants (2, 1, 0.5 and 0.1 bar). This spectrum of dispersion energies had been shown to characterise the level of cohesion within a test powder, and to be a good predictor of aerosolisation behaviour in a passive DPI. . Data were presented in the form of particle size distribution and the changes in d50 and d97 values as a function of dispersion energy. d50 is the particle size measured by Malvern, for which 50% of the particles by volume are less than this size. d97 is the particle size measured by Malvern, for which 97% of the particles by volume are less than this size.

Formulations were processed using:

1) The Hosokawa Micron Mechano-Fusion AMS Mini system. This system was operated with a novel rotor, providing a 1mm compression gap; and

2) The Hosokawa Micron AS50 spiral jet mill.

The in-vitro testing was performed using an Aspirair (trade mark) device.

The formulations were composed of one or more of the following constituents:

Magnesium stearate (standard grade)
L-Leucine (Ajinomoto) and jet milled by Micron Technologies
Sorbolac 400 lactose
Micronised clobozam
Micronised apomorphine hydrochloride
Micronised lactose
Re-condensed Leucine (Aerocine)

Mechano-Fused Formulations including Additive Material

19.0g of Sorbolac 400 lactose and 1.0g of micronised L-leucine were combined in the Mechano-Fusion system. The material was processed at a setting of 20% power for 5 minutes, followed by a setting of 80% power for 10 minutes. This material was given the reference "1A".

A batch of micronised apomorphine hydrochloride was gently pressed through a 212µm metal sieve, using the rounded face of a metal spatula. 3.6g of this was then combined with 14.4g of "1A" in the Mechano-Fusion system. The material was processed at a setting of 20% power for 5 minutes. After blending, this powder was rested overnight, and then was gently pushed through a 300µm metal sieve with a spatula. This material was recorded as "1B".

The content uniformity of this blend was assessed by taking 10 approximately 2mg samples, recording the weights on a 4 figure balance, and then assaying for drug content by HPLC. The "1B" batch had an average drug content of 22.6%, with relative standard deviation of 4.0%.

19.0g of Sorbolac 400 lactose and 1.0g of micronised L-leucine were combined in the Mechano-Fusion system. The material was processed at a setting of 20% power for 5 minutes, followed by a setting of 80% power for 10 minutes. This material was recovered and recorded as "2A".

15.0g of apomorphine hydrochloride and 0.75g of micronised L-leucine were combined in the Mechano-Fusion system. The material was processed at a setting

of 20% power for 5 minutes, followed by a setting of 80% power for 10 minutes. This material was recovered and recorded as "2B".

4.2g of "2B" was then combined with 15.8g of "2A" in the Mechano-Fusion system. The material was processed at a setting of 20% power for 5 minutes. After blending, this powder was rested overnight, and then was gently pushed through a 300µm metal sieve with a spatula. This material was recorded as "2C".

The content uniformity of this blend was assessed by taking 10 approximately 2mg samples, recording the weights on a 4 figure balance, and then assaying for drug content by HPLC. The "2C" batch had an average drug content of 23.5%, with relative standard deviation of 3.2%.

A number of foil blisters were filled with approximately 2mg of "1B" and "2C". These were then fired from an Aspirair device into an NGI at a flow rate of 60l/m. The Aspirair was operated with a reservoir of 15ml of at 1.5 bar. This in vitro test was conducted 3 times. The results are summarised in Tables 1 and 2 below.

Table 1

Formulation	MD (mg)	DD (mg)	FPD (<5µm) (mg)	FPF % (<5µm)	MMAD
1B	335	309	200	65	1.36
	367	349	210	60	1.67
	334	308	184	60	1.42
2C	453	412	214	52	1.51
	432	387	196	51	1.55
	396	357	164	46	1.81

Table 2 (* Percentages of MD)

Formulation	*recovery	*throat	*blister	*device
1B	74%	25%	4%	1%
	81%	28%	3%	1%
	74%	30%	5%	2%
2C	96%	35%	7%	1%
	92%	35%	7%	1%
	84%	39%	8%	1%

These initial tests on the first apomorphine HCl formulations, showed device retention was reduced in comparison with the concurrent non-FCA formulations. Also, very fine MMADs indicated near perfect dispersion. However, when the Mechano-Fused particles were dispersed, these benefits were offset by substantially increased throat deposition.

Comparison of Co-Jet Milled and Mechano-Fused Formulations (Clobozam)

1.01g of micronised clobozam was weighed out, and then gently pressed through a 300µm metal sieve, using the rounded face of a metal spatula. This formulation was recorded as "3A".

9.37g of micronised clobozam was then combined with 0.50g of micronised L-leucine in the Mechano-Fusion system. The material was processed at a setting of 20% power for 5 minutes, followed by a setting of 80% power for 10 minutes. This material was recorded as "4A". After blending, this powder was then gently pushed through a 300µm metal sieve with a spatula. This material was recorded as "4B".

9.57g of micronised clobozam was then combined with 0.50g of magnesium stearate in the Mechano-Fusion system. The material was processed at a setting of 20% power for 5 minutes, followed by a setting of 80% power for 10 minutes. This material was recorded as "5A". After blending, this powder was rested overnight, and then was gently pushed through a 300µm metal sieve with a spatula. This material was recorded as "5B".

9.5g of micronised clobozam was then combined with 0.50g of micronised L-leucine in the Mechano-Fusion system. The material was processed at a relatively low speed setting of 20% power for 5 minutes. This process was intended only to produce a good mix of the components. This material was recorded as "6A".

6.09g of "6A" fed at approximately 1g per minute into an AS50 spiral jet mill, set with an injector pressure of about 7 bar and a grinding pressure of about 5 bar. The resulting material was recovered and recorded as "6B".

After milling, this powder was rested overnight, and then was gently pushed through a 300μm metal sieve with a spatula. This material was recorded as "6C".

9.5g of micronised clobozam was then combined with 0.50g of magnesium stearate in the Mechano-Fusion system. The material was processed at a setting of 20% power for 5 minutes. This material was recorded as "7A".

6.00g of "7A" was fed at approximately 1g per minute into the AS50 spiral jet mill, set with an injector pressure of about 7 bar and a grinding pressure of about 5 bar. The resulting material was recovered and recorded as "7B".

After milling, this powder was gently pushed through a 300μm metal sieve with a spatula. This material was recorded as "7C".

A batch of re-condensed leucine (also referred to as "Aerocine") was produced by subliming to vapour a sample of leucine in a tube furnace, and re-condensing as a very finely dispersed powder as the vapour cooled. This batch was identified as "8A".

9.5g of micronised clobozam was then combined with 0.50g of Aerocine, in the Mechano-Fusion system. The material was processed at a setting of 20% power for 5 minutes, followed by a setting of 80% power for 10 minutes. . This material was recorded as "8B". After blending, this powder was rested overnight, and then was gently pushed through a 300μm metal sieve with a spatula. This material was recorded as "8C".

9.5g of micronised clobozam was combined with 0.50g of Aerocine in the Mechano-Fusion system. The material was processed at a setting of 20% power for 5 minutes. 7.00g of this powder was then fed into the AS50 spiral jet mill, set with an injector pressure of about 7 bar and a grinding pressure of about 5 bar. The resulting material was recovered and recorded as "9A".

After milling, this powder was gently pushed through a 300μm metal sieve with a spatula. This material was recorded as "9B".

A number of foil blisters were filled with approximately 2mg of the following formulations:

3A - no milling & no FCA
4B - leucine & Mechano-Fused
5B - magnesium stearate & Mechano-Fused
6C - leucine & co-jet milled
7C - magnesium stearate & co-jet milled
8C - Aerocine & co-jet milled
9B - Aerocine & Mechano-Fused.

These formulations were then fired from an Aspirair device into an NGI at a flow rate of 60l/m. The Aspirair was operated under 2 conditions for each formulation: with a reservoir of 15ml of air at 1.5 bar or with a reservoir of 30ml of air at 0.5 bar. These in vitro tests were conducted in each case once to screen, and then the selected primary candidate was retested.

Through life dose uniformity for the selected candidate was tested by firing 30 doses, with the emitted doses collected by DUSA.

Full details of the results are attached. The impactor test results are summarised in Tables 3, 4 and 5 below.

Table 3

Formulation	MD (mg)	DD (mg)	FPD(mg) (<5µm)	MMAD
3A 0.5 bar 30ml	2.04	1.12	0.88	2.91
3A 1.5 bar 15ml	1.92	1.74	1.23	2.86
4B 0.5 bar 30ml	1.84	1.48	0.82	3.84
4B 1.5 bar 15ml	1.80	1.56	0.81	3.32
5B 0.5 bar 30ml	1.84	1.53	1.17	2.34
5B 1.5 bar 15ml	1.85	1.55	1.12	2.22
6C 0.5 bar 30ml	1.93 1.86	1.80 1.73	1.67 1.62	2.11 2.11
6C 1.5 bar 15ml	1.85 1.97	1.76 1.86	1.61 1.67	1.26 2.07
6C 1.5 bar 15ml (silicon coated plates)	1.74	1.65	1.46	2.03
7C 0.5 bar 30ml	2.06	1.99	1.87	1.97
7C 1.5 bar 15ml	1.89	1.78	1.63	1.79
8C 0.5 bar 30ml	1.82	1.73	1.62	2.02
8C 1.5 bar 15ml	1.81	1.74	1.57	2.01
9B 0.5 bar 30ml	1.88	1.73	1.04	3.48
9B 1.5 bar 15ml	1.80	1.64	0.94	3.12

Table 4

Formulation	FPF(MD) % (<5μm)	FPF(ED) % (<5μm)	FPF(ED) % (<3μm)	FPF(ED) % (<2μm)	FPF(ED) % (<1μm)
3A 0.5 bar 30ml	43	78	49	32	17
3A 1.5 bar 15ml	64	71	45	24	6
4B 0.5 bar 30ml	45	55	28	15	7
4B 1.5 bar 15ml	45	52	30	18	9
5B 0.5bar 30ml	64	77	54	42	30
5B 1.5 bar 15ml	61	72	52	38	25
6C 0.5 bar 30ml	87 87	93 94	77 76	44 44	8 9
6C 1.5 bar 15ml	87 85	91 90	89 73	79 44	27 10
6C 1.5 bar 15ml (silicon coated plates)	84	89	74	45	8
7C 0.5 bar 30ml	91	94	79	50	14
7C 1.5 bar 15ml	86	92	82	56	16
8C 0.5 bar 30ml	89	93	79	48	12
8C 1.5 bar 15ml	87	90	76	46	9
9B 0.5 bar 30ml	55	60	34	24	15
9B 1.5 bar 15ml	52	57	34	24	15

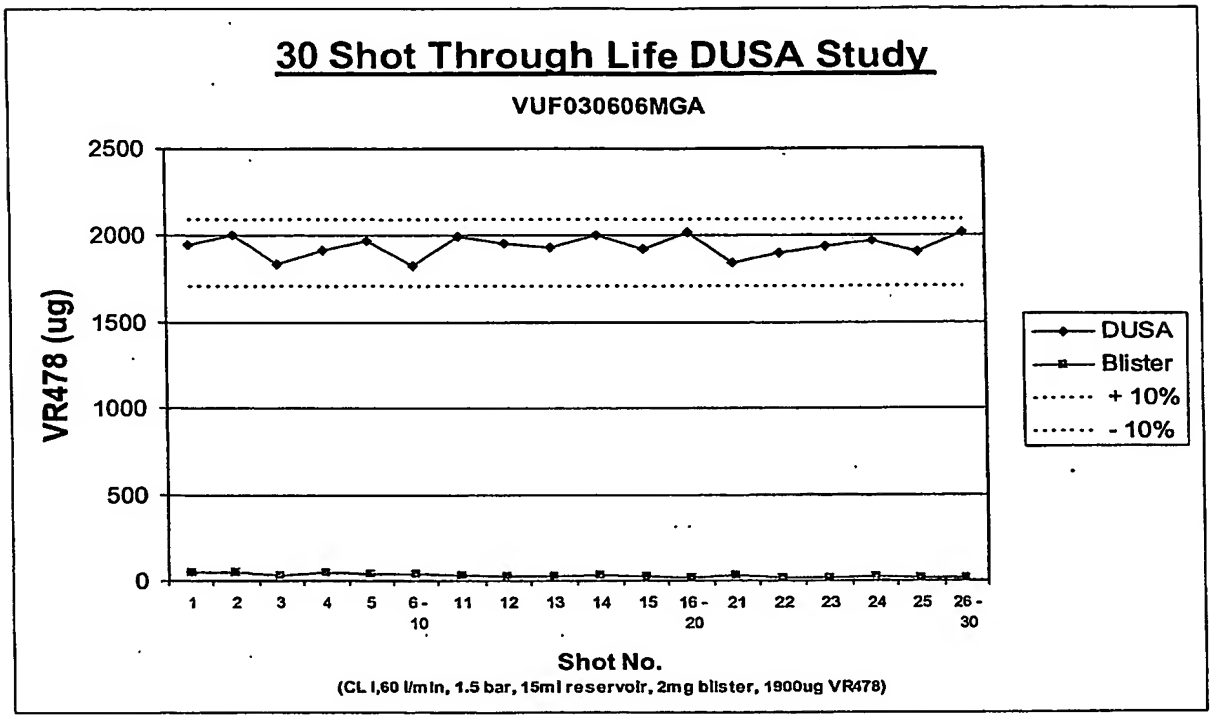
Table 5

Formulation	*recovery	*throat	*blister	*device
3A 0.5 bar 30ml	102%	3%	1%	43%
3A 1.5 bar 15ml	96%	15%	1%	8%
4B 0.5 bar 30ml	97%	15%	7%	12%
4B 1.5 bar 15ml	95%	27%	6%	8%
5B 0.5 bar 30ml	97%	7%	13%	4%
5B 1.5 bar 15ml	98%	14%	12%	4%
6C 0.5 bar 30ml	97% 101%	2% 3%	1% 1%	6% 5%
6C 1.5 bar 15ml	99% 104%	6% 6%	1% 3%	4% 3%
6C 1.5 bar 15ml (silicon coated plates)	91%	8%	1%	4%
7C 0.5 bar 30ml	110%	2%	1%	3%
7C 1.5 bar 15ml	99%	6%	2%	3%
8C 0.5 bar 30ml	99%	3%	1%	4%
8C 1.5 bar 15ml	95%	6%	1%	3%
9B 0.5 bar 30ml	96%	16%	2%	7%
9B 1.5 bar 15ml	95%	26%	4%	5%

From these results it can be seen that the co-jet milled formulations exhibited exceptional FPFs, which were significantly better that those of the Mechano-Fused formulations. This improvement would appear to be largely due to reduced throat deposition, which was less than 8% for the co-jet milled formulations, compared to 15% for the pure drug and up to 27% for the Mechano-Fused formulations.

Through life dose uniformity for the primary candidate, 6C,

was tested by firing 30 doses, with the emitted doses collected by DUSA. Through life dose uniformity results are presented below:



The mean ED was 1965 µg, with an RSD of 2.8%.

This material consequently demonstrated excellent through life dose reproducibility.

The results of dispersion testing of these powdered materials are provided in the Figures. The particle size distributions indicate both the level of size reduction obtained by the co-milling, and the level of dispersion efficiency at varied pressures. The d50 and d97 plots provide a further indication of this dispersibility of the powders as a function of pressure.

The graphs in Figures 1A to 6A figures show the particle size distribution, with the four curves representing powder jet-milled at different pressures, namely at 2.0 bar, 1.0 bar, 0.5 bar and at 0.1 bar. The graphs in Figure 1B to 6B show the level of dispersion efficiency at different pressures, in terms of d50 and d97.

Figures 1A and 1B are the results of testing formulation "3A".
Figures 2A and 2B are the results of testing formulation "4B".
Figures 3A and 3B are the results of testing formulation "5B".
Figures 4A and 4B are the results of testing formulation "6C".
Figures 5A and 5B are the results of testing formulation "7C".
Figures 6A and 6B are the results of testing formulation "8C".
Figures 7A and 7B are the results of testing formulation "9B".

From the graphs, one can see that formulation 5B exhibited much the best dispersion.

This set of dispersibility tests shows that the MechanoFused powders disperse more easily at lower pressures than the original drug, and that magnesium stearate gives the best dispersion within these, followed by Aerocine and leucine. The co-jet milled powders do not appear to disperse any more easily in this test than the original drug, however the primary particle sizes (d50) are reduced.

Comparison of Co-Jet Milled and Mechano-Fused Formulations (Apomorphine)

Next, in order to establish the effect of co-jet milling on different active agent, further apomorphine hydrochloride formulations were prepared and tested.

2.1g "2B" plus 0.4g micronised leucine were blended by hand in a mortar and pestle for 2 minutes. 2.5g micronised lactose was added and blended for a further 2 minutes. 5g micronised lactose was added and blended for another 2 minutes. This mixture was then processed in the AS50 Spiral jet mill using an inlet pressure of 7 bar and a grinding pressure of 5 bar, feed rate 5ml/min. This powder was gently pushed through a 300μm metal sieve with a spatula. This material was recorded as "10A".

1.5g "10A" was combined with 0.20g micronised L-leucine and 3.75g of Sorbolac 400 lactose by hand in a mortar with a spatula for 10 minutes. This powder was

gently pushed through a 300μm metal sieve with a spatula. This material was recorded as "10B".

9g micronised apomorphine HCl plus 1g micronised leucine were placed in the Mechano-Fusion system and processed at 20% (1000rpm) for 5 minutes. This initial blend was then processed in the AS50 Spiral jet mill using an inlet pressure of 7 bar and a grinding pressure of 5 bar, feed rate 5ml/min. This material was recorded as "11A".

After blending, this powder was rested overnight, and then was gently passed through a 300μm metal sieve by shaking. This material was recorded as "11B".

2g micronised apomorphine HCl plus 0.5g micronised leucine were blended by hand in mortar and pestle for 2 minutes. 2.5g micronised lactose was added and blended for a further 2 minutes. Then 5g micronised lactose was added and blended for another 2 minutes. This mixture was then processed in the AS50 Spiral jet mill using an inlet pressure of 7 bar and a grinding pressure of 5 bar, feed rate 5ml/min. This powder was gently pushed through a 300μm metal sieve with a spatula. This material was recorded as "12A".

16.5g of Sorbolac 400 and 0.85g of micronised leucine were placed in the Mechano-Fusion system and processed at 20% (1000rpm) for 5 minutes then at 80% (4000rpm) for 10 minutes. This material was recorded as "13A".

0.5g micronised apomorphine HCl plus 2.0g "13A" were blended by hand in a mortar with a spatula for 10 minutes. This powder was gently pushed through a 300μm metal sieve with a spatula. This material was recorded as "13B".

A number of foil blisters were filled with approximately 2mg of the following formulations:

10A - 20% apomorphine HCl, 5% l-leucine, 75% micronised lactose (co-jet milled)
10C - 26.2% apomorphine HCl, 5% l-leucine, 68.7% sorbolac (geometric)

11B - 95% apomorphine HCl, 5% l-leucine (co-jet milled)

12A - 20% apomorphine HCl, 5% leucine, 75% micronised lactose (all co-jet milled)

13B - 20% apomorphine HCl, 5% l-leucine, 75% Sorbolac 400 (leucine & Sorbolac Mechano-Fused)

These were then fired from an Aspirair device into an NGI at a flow rate of 60l/m. The Aspirair was operated with a reservoir of 15ml of at 1.5 bar. Each in vitro test was conducted once to screen, and then the selected candidates were repeated. Further candidates were also repeated in ACI at 60 l/m.

Through life dose uniformity for the selected candidates was tested by firing 30 doses, with the emitted doses being collected.

Table 6

Formulation **2mg, 1.5 bar** **15ml reservoir** **60 l/min**	**MD (µg)**	**DD (µg)**	**FPD (<5µm) (µg)**	**MMAD**
10A WHAT ARE THESE FIGURES???	384 (1920)	356 (1780)	329 (1645)	1.78
13B	359 (1793)	327 (1635)	200 (1000)	1.54
10C	523	492	374	1.63
11B	1891 1882 1941 1905 32 1.7	1680 1622 1669 1657 31 1.9	1614 1551 1601 1589 33 2.1	1.36 1.44 1.49 1.43 0.07 4.6
11B <u>ACI</u> Ave. SD RSD	1895 1895 1923 1904 16 1	1559 1549 1565 1558 8 1	1514 1485 1504 1501 15 1	1.58 1.62 1.62 1.61 0.02 1
12A	414 410 406 410 4 1 2050	387 387 378 384 5 1 1920	363 363 355 360 5 1 1800	1.63 1.66 1.68 1.66 0.03 2
12A <u>ACI</u> Ave. SD RSD Total ave.	395 411 400 402 8 2 2011	365 385 370 373 10 3 1866	341 360 349 350 10 3 1750	1.80 1.85 1.84 1.83 0.04 2

Table 7

Formulation 2mg, 1.5 bar 15ml reservoir 60 l/min	FPF(MD) % (<5um)	FPF(ED) % (<5um)	FPF(ED) % (<3um)	FPF(ED) % (<2um)	FPF(ED) % (<1um)
10A	86	93	87	60	13
13B	56	61	52	42	19
10C	72	76	67	51	16
11B	85	96	95	81	24
	82	96	93	77	22
	82	96	92	74	20
Ave.	83	96	93	77	22
SD		0	1.5	3.5	2
RSD		0	1.6	4.5	9.1
11B	80	97	94	74	14
	78	96	93	70	14
	78	96	94	72	12
ACI					
Ave.	79	96	94	72	13
SD		1	1	2	1
RSD		1	1	3	9
12A	88	94	89	68	13
	89	94	89	66	12
	87	94	88	64	12
Ave.	88	94	89	66	12
SD		0	1	2	1
RSD		0	1	3	5
12A	86	94	85	57	9
	88	93	84	55	8
	87	94	85	56	8
ACI					
Ave.	87	94	85	56	8
SD		1	1	1	1
RSD		1	1	2	7

Table 8

Formulation 2mg, 1.5 bar 15ml reservoir 60 l/min	Recovery	Throat	Blister	Device
10A	96%	5%	0.3%	7%
13B	94%	29%	3%	6%
10C	100%	16%	2%	4%
11B	101%	2%	0.6%	10%
	99%	2%	0.2%	14%
	102%	2%	0.3%	14%
Ave.	101%	2%	0.4%	13%
SD	1.5	0	0.2	2.3
RSD	1.5	0	57	18
11B	100%	1%	0.5%	17%
	100%	2%	0.1%	18%
	101%	2%	0.4%	18%
ACI				
Ave.	100%	2%	0.3%	18%
SD	1	1	0.2	1
RSD	1	35	62	3
12A	109%	4%	0.3%	6%
	108%	4%	0.2%	6%
	107%	4%	0.02%	7%
Ave.	108	4%	0.2	6%
SD	1	0	0.1	1
RSD	1	0	82	9
12A	104%	3%	0.4%	7%
	108%	4%	0.2%	6%
	105%	2%	0.4%	7%
ACI				
Ave.	106%	3%	0.3	7%
SD	2	1	0.1	1
RSD	2	33	35	9

The co-jet milled formulations once again exhibited exceptional FPFs, with the improvement largely due to reduced throat deposition which was less than 5%, compared to between 16 and 29% for the Mechano-Fused formulations. "12A" was produced as a repeat of "10A", but excluding the Mechano-Fused pre-blend (to show it was not required).

In order to investigate the cause of the unexpected differences between the co-jet milled formulations and those prepared by Mechano-Fusion, formulations "11B", "10A" and "2C" were fired from an Aspirair and plume and vortex behaviour recorded on digital video. The images were studied in light of the above differences in throat deposition.

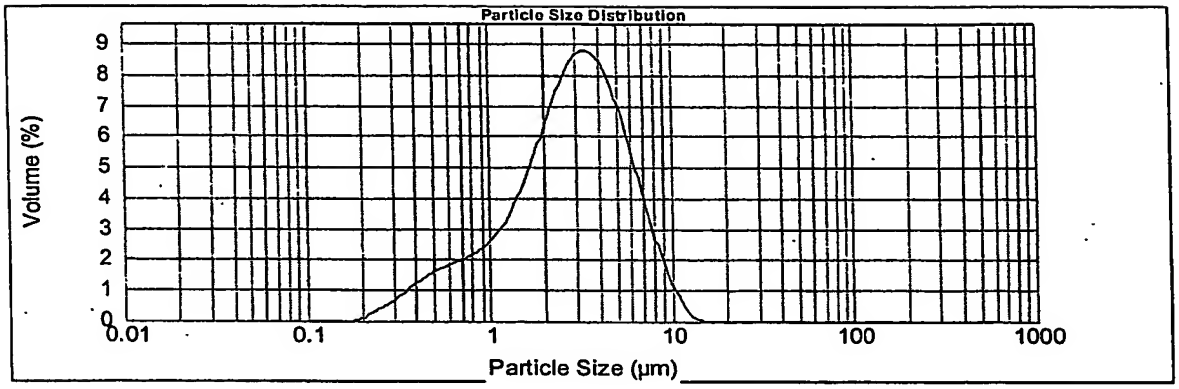
Video of plume behaviour indicated a difference between the co-jet milled formulations and Mechano-Fused formulations. Mechano-Fused formulations showed a highly concentrated fast moving bolus at the front of the air jet. Most powder appeared to have been emitted after approximately 40ms. Co-jet milled formulations showed a greater spread of the plume. The plume front moves at a similar velocity, but the front is less concentrated, appears to slow more quickly and powder is emitted for considerably longer (i.e. >200ms).

Video of the vortex showed that the Mechano-Fused powders enter the vortex within 10ms, whereas co-jet milled formulations take at least 30ms. Similarly the Mechano-Fused powders appeared quicker to leave the vortex, with the co-jet milled materials forming a more prolonged fogging of the vortex. Greater device 'stick and scour' behaviour was also observed for co-jet milled materials.

Particle size distributions of the raw materials and selected formulations were determined by Malvern particle sizer, via the Scirroco dry powder disperser. The data are summarised below:

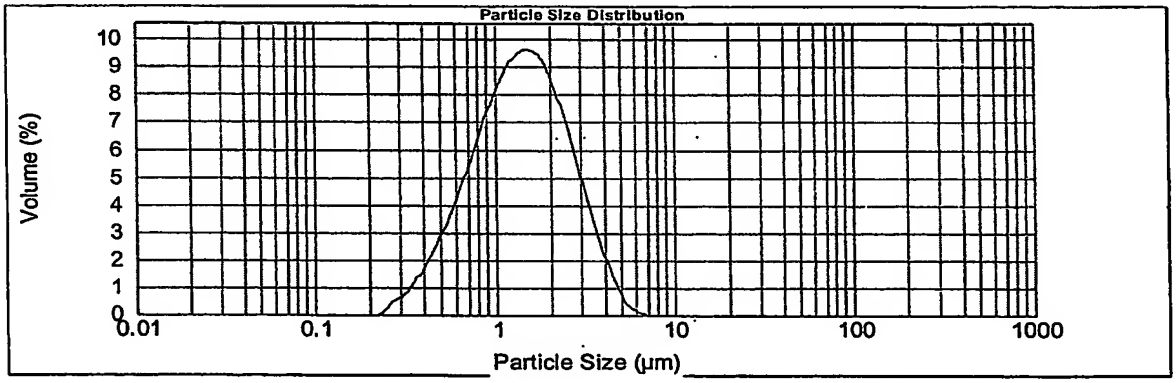
Raw Materials

Micronised lactose (833704)



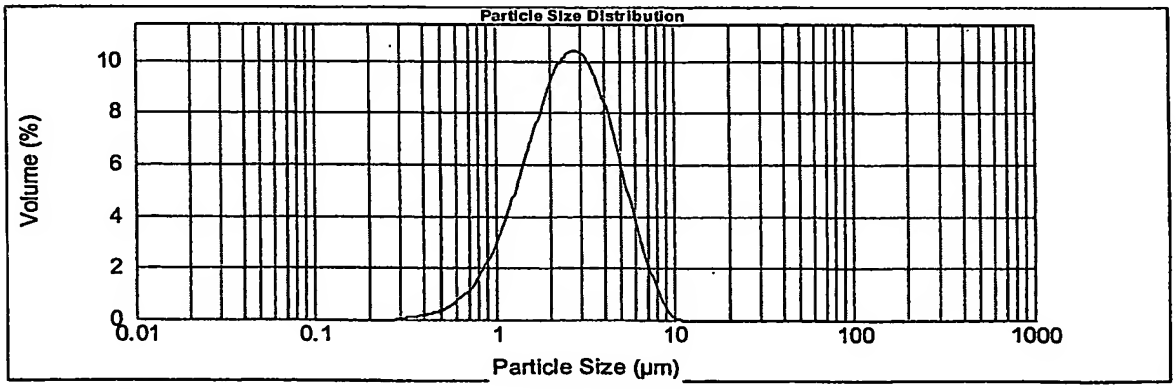
d(0.5) 2.8µm d(0.9) 6.3µm D[4,3] 3.3µm

Apomorphine



d(0.5) 1.4µm d(0.9) 2.9µm D[4,3] 1.6µm

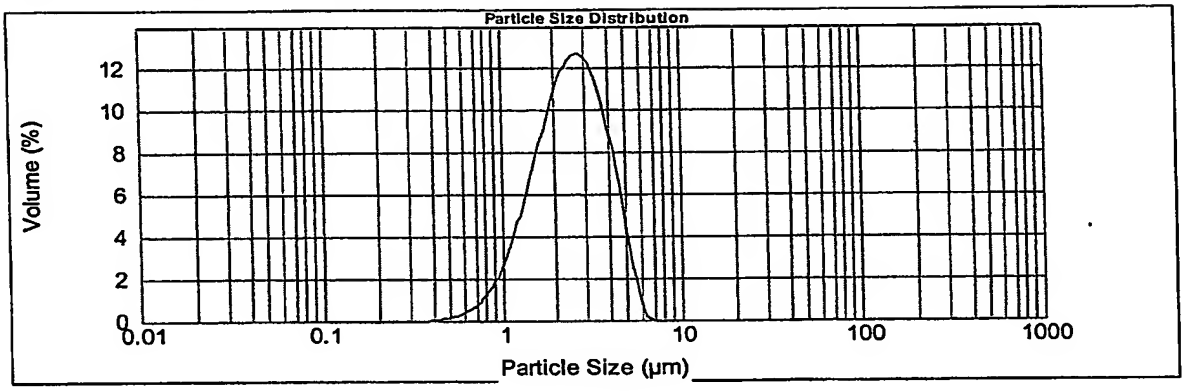
Clobozam



d(0.5) 2.6µm d(0.9) 5.2µm D[4,3] 2.9µm

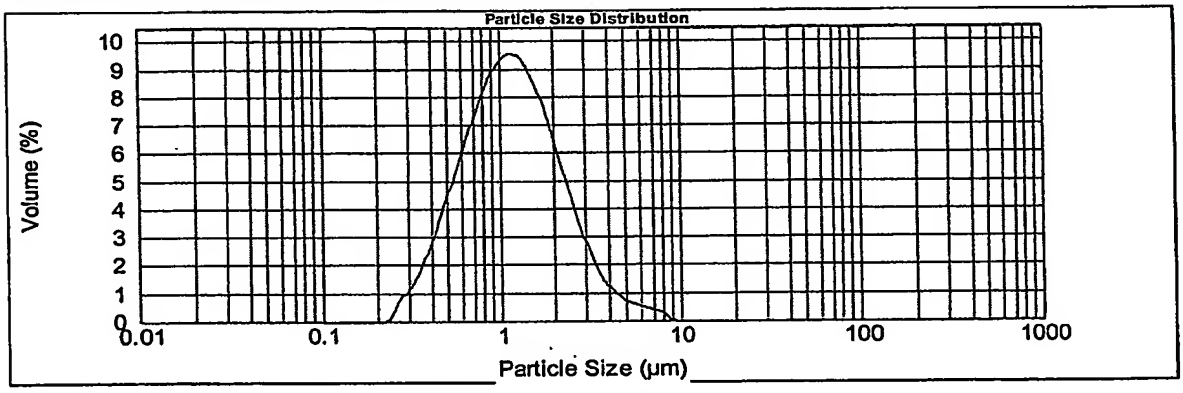
Clobozam Formulations

(95% Clobozam, 5% MgSt MechanoFused)



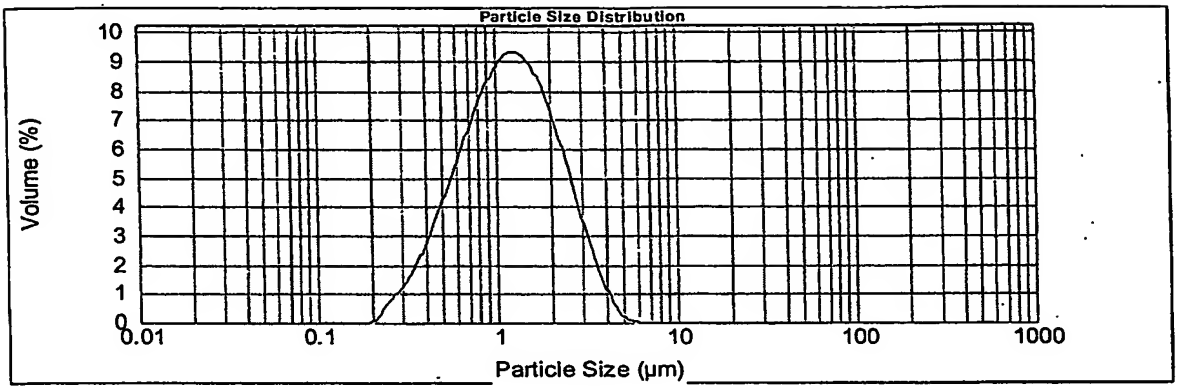
d(0.5) 2.5µm d(0.9) 4.2µm D[4,3] 2.6µm

(95% Clobozam, 5% Aerocine, Co-jet milled)



d(0.5) 1.1µm d(0.9) 2.6µm D[4,3] 1.4µm

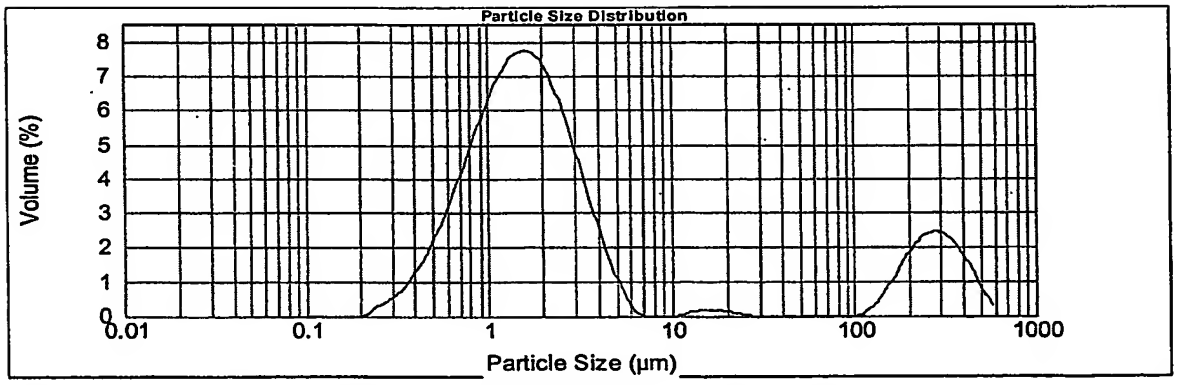
(95% Clobozam, 5% leucine, Co-jet milled)



d(0.5) 1.2µm d(0.9) 2.5µm D[4,3] 1.4µm

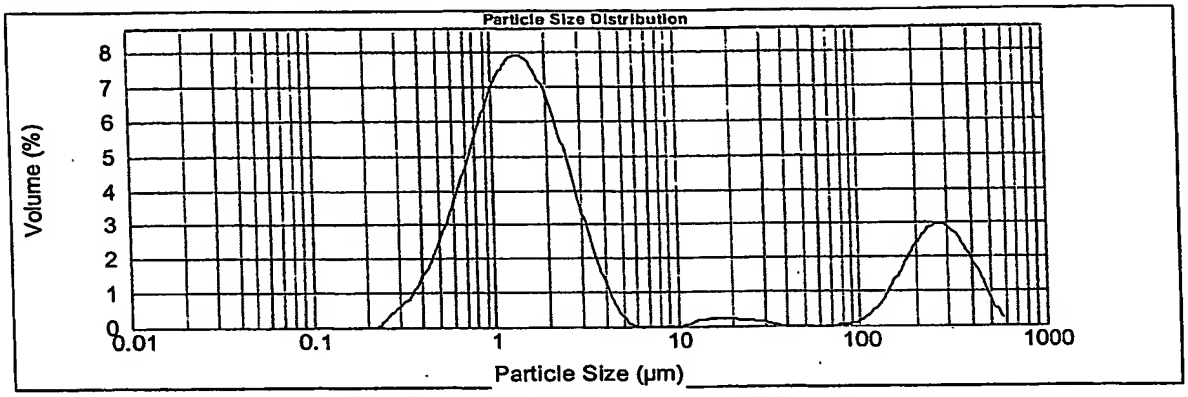
Apomorphine Formulations

(75% lactose, 20% Apomorphine, 5% leucine, Co-jet milled)



d(0.5) 1.8µm d(0.9) 243.6µm D[4,3] 38.0µm

(75% lactose, 20% Apomorphine, 5% leucine, Co-jet milled)



d(0.5) 1.6µm d(0.9) 261.0µm D[4,3] 55.8µm

Where clobozam is co-milled with FCA, a significant drop in particle size is observed. This is not seen for the clobozam MechanoFused formulation here.

With the apomorphine-lactose co-milled materials, the size distribution is reduced, when compared to the particle size distribution of the micronised lactose which comprises 75% of the composition. However, size reduction is not as great with respect to pure apomorphine.

In vitro data confirm that Mechano-Fusion of active particles increased the throat deposition substantially. The higher the intensity of Mechano-Fusion used, the greater the apparent throat deposition. Increasing intensity of Mechano-Fusion has previously been associated with improvement in dispersibility. However, in this case, Mechano-Fusion with magnesium stearate gives lower throat deposition than Mechano-Fusion with leucine, and magnesium stearate generally gives improved dispersibility. Consequently, it is not a simple effect on dispersibility of the powder.

The throat deposition appears especially high for Mechano-Fused formulations containing leucine. It is speculated that this could be due to an agglomerating affect during Mechano-Fusion specific to leucine and not magnesium stearate, or an electrostatic effect specific to leucine.

However, co-jet milling produces materials which give very low throat deposition, low device deposition and excellent dispersion. This co-jet milling also produces a significant further size reduction: d50 changes from about 2μm to about 1μm. When these factors are combined, a remarkable aerosolisation performance is obtained from the in-vitro tests. FPF(ED) are 90 to 96%. This excellent performance was obtained for leucine, Aerocine and magnesium stearate, and for 3 different formulations, including 2 different active agents, with or without lactose diluent.

It was noted that the co-jet milled materials were highly agglomerated in appearance, in contrast to the Mechano-Fused blends, which appeared as more free flowing powders.

Studies suggest that the difference between the performance of the co-jet milled and Mechano-Fused compositions is most apparent when the formulations are dispensed using an active device, such as Aspirair. Video of plume behaviour provided some indication of the reason for differences between the co-jet milled formulations and Mechano-Fused formulations. Mechano-Fused formulations showed a short fast bolus, whereas co-jet milled formulations showed a more drawn out plume. The "enhanced" flow properties of the Mechano-Fused powders appear to explain their worse Aspirair performance. A degree of powder hold-up appears to be beneficial.

These video observations suggest the throat deposition difference is related to the powder lifetime within the vortex, with a longer lifetime giving reduced deposition. This does not lead to a complete explanation or understanding of why such a large reduction in throat deposition is seen. However, lower aerosol concentration at plume front, lower momentum of aerosol plume (with lower cloud density and smaller particle size) and greater opportunity to be de-agglomerated are possible contributors.

In general, the co-milling of active particles with additive particles has yielded reduced device/blister retention compared to formulations prepared without additive particles. Mechano-Fusion was shown to give significantly greater blister retention than co-jet milling. The worst blister retention was seen for Mechano-Fused clobozam with magnesium stearate (13%). This appears related to the dusting nature of such formulations. The Mechano-Fused powders spread and flow more easily, which facilitates higher degrees of contact with the surfaces in bulk powder contact. The co-milled powders however are heavily agglomerated, so contact with surfaces is much reduced, and dust residues are also much less. The device retention also appears greater for Mechano-Fused than co-jet milled powders for clobozam. However, the device retention of apomorphine HCl co-jet milled with leucine appears notably high, at 13%. Device and blister retention does not appear substantially different between the 0.5 and 1.5 bar tests, except for the pure clobozam, where device retention approaches 50% for the 0.5 bar test.

It has also been discovered that the co-jet milling of active particles and additive particles has the added advantage that the additive particles act as a milling aid and actually enhance the milling action of the jet mill. In particular, it is believed that the additive particles are able to force open cracks on the surfaces of the active particles, assisting in the breaking apart of the active particles. This is another unexpected advantage, as this had not been observed when co-milling active and additive particles using other milling techniques.

The use of milling aids in milling (especially of pharmaceutical compositions) has generally been avoided as the milling agents are considered to be a potential source of contamination. Clearly, it would be unacceptable for a pharmaceutical composition intended for pulmonary inhalation to include any contaminants.

The finding that the additive materials of the present invention can act as milling aids when jet milling is particularly pleasing, as this means that the co-jet milling not only results in composite active particles, but also in particles of smaller particle size than achieved without the additive particles.

The reduction in particle size may also be increased by carrying out the co-jet milling at lower temperatures. Whilst the co-jet milling process may be carried out at temperatures between -20°C and 40°C, the particles will tend to be more brittle at lower temperatures, and they therefore fracture more readily so that the milled particles tend to be even smaller.

The optimum amount of additive material will depend on the chemical composition and other properties of the additive material and upon the nature of the active material and/or excipient material, if present. In general, the amount of additive material in the composite active particles will be not more than 60% by weight, based on the weight of the active material and any excipient material. However, it is thought that for most additive materials the amount of additive material should be in the range of 40% to 0.25%, preferably 30% to 0.5%, more preferably 20% to 2%, based on the total weight of the additive material and the active material being milled. In general, the amount of additive material is at least 0.01% by weight based on the weight of the active material.

Co-jet milling may be carried out at pressures between 0.1 and 12 bar. Varying the pressure allows one to control the degree of particle size reduction. At pressures in the region of 0.1-3 bar, and preferably 1-2 bar, the co-jet milling will primarily result in blending of the active and additive particles, so that the additive material coats the active particles. On the other hand, at 3-12 bar, and preferably 5-12 bar, the co-jet milling will additionally lead to particle size reduction.

Tests were carried out whereby pre-micronised lactose (as a drug model) was co-jet milled in an MC50 Hosakawa Micron with 5% magnesium stearate. At 2 bar milling pressure, the resultant material had a d50 of approximately 3μm, whilst milling the same mixture at around 7 bar resulted in material with a d50 of about 1μm. Thus, when operating with a jet milling pressure of 0.1-3 bar little milling, that it is particle size reduction, is seen. From 3-12 bar milling pressure, increasing milling is seen, with the particle size reduction increasing with the increasing pressure. This means that the milling pressure may be selected according to the desired particle size in the resultant mixture.

Clearly, many different designs of jet mills exist and any of these may be used in the present invention. For example, in addition to the AS50 Spiral jet mill and the MC50 Hosakawa Micron used in the experiments discussed above, one can also use other spiral jet mills, pancake jet mills or opposed fluid bed jet mills. The feed rate for the jet mills will depend on their size. Small spiral jet mills might use a feed rate of, for example, 1 to 2g per minute, whilst industrial scale mills will have a feed rate in the order of kilograms per hour.

Claims

1. A method for making composite active particles for use in a pharmaceutical composition for pulmonary inhalation, the method comprising jet milling active particles in the presence of particles of additive material and, optionally, air or a compressible gas or fluid.

2. A method as claimed in claim 1, wherein the additive material comprises an amino acid, a metal stearate or a phospholipid.

3. A method as claimed in claim 2, wherein the additive material comprises one or more of leucine, isoleucine, lysine, valine, methionine, phenylalanine.

4. A method as claimed in claim 3, wherein the additive material comprises leucine and preferably L-leucine.

5. A method as claimed in claim 2, wherein the additive material comprises magnesium stearate.

6. A method as claimed in claim 2, wherein the additive material comprises lecithin.

7. A method as claimed in any one of the preceding claims, wherein the jet milling is carried out at an inlet pressure of between 0.1 and 3 bar.

8. A method as claimed in any one of claims 1-6, wherein the jet milling is carried out at an inlet pressure of between 3 and 12 bar.

9. A method as claimed in any one of the preceding claims, wherein at least 90% by volume of the active particles are less than 20μm in diameter prior to jet milling.

10. A method as claimed in any one of the preceding claims, wherein at least 90% by volume of the additive particles are less than 20μm in diameter prior to jet milling.

11. A method as claimed in any one of the preceding claims, wherein jet milling is carried out at temperatures below room temperature.

12. A method as claimed in claim 11, wherein jet milling is carried out at a temperature below 10°C and preferably below 0°C.

13. Composite active particles for use in a pharmaceutical composition made using a method as claimed in any one of the preceding claims.

14. Composite active particles as claimed in claim 13, for pulmonary inhalation.

15. Composite active particles as claimed in either of claims 13 and 14, wherein the additive material forms a coating on the surface of the additive particles.

16. Composite active particles as claimed in claim 15, wherein the coating is a discontinuous coating.

17. Composite active particles as claimed in either of claims 15 and 16, wherein the coating of additive material is not more than 1μm in thickness.

18. Composite active particles as claimed in any one of claims 13-17, having a MMAD of not more than 10μm.

19. Composite active particles as claimed in claim 18, having a MMAD of not more than 5μm, not more than 3μm, not more than 2μm, or not more than 1μm.

20. Composite active particles as claimed in any one of claims 13-19, wherein at least 90% by weight of the composite active particles have a diameter of not more than 10μm.

21. Composite active particles as claimed in claim 20, wherein at least 90% by weight of the particles have a diameter of not more than 5μm, not more than 3μm, or not more than 1μm.

22. A pharmaceutical composition comprising composite active particles as claimed in any one of claims 13-21.

23. A composition as claimed in claim 22, wherein the composition is for pulmonary inhalation.

24. A composition as claimed in either of claims 22 and 23, wherein the composition is a dry powder composition.

25. A composition as claimed in claim 24, wherein the composition further comprises carrier particles.

26. A composition as claimed in any one of claims 22-25, wherein the composition has a FPF(ED) of at least 70%.

27. A composition as claimed in claim 26, wherein the FPF(ED) is at least 80%, at least 85%, or at least 90%.

28. A composition as claimed in any one of claims 22-25, wherein the composition has a FPF(MD) of at least 60%.

29. A composition as claimed in claim 26, wherein the FPF(MD) is at least 70%, at least 80%, or at least 85%.

30. A dry powder inhaler containing a composition as claimed in any one of claims 22-29.

31. Use of an additive material as a milling aid in the jet milling of an active material.

Abstract

Manufacture of Pharmaceutical Compositions

The present invention relates to particles and to methods of making particles. In particular, the invention relates to methods of making composite active particles comprising a pharmaceutically active material for pulmonary inhalation, the method comprising a jet milling process.

Figure 1A

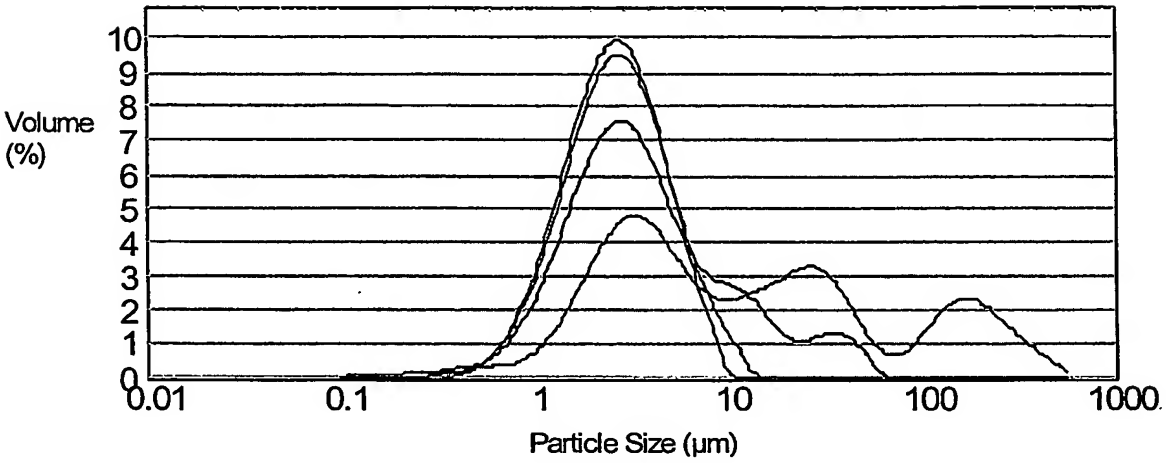


Figure 1B

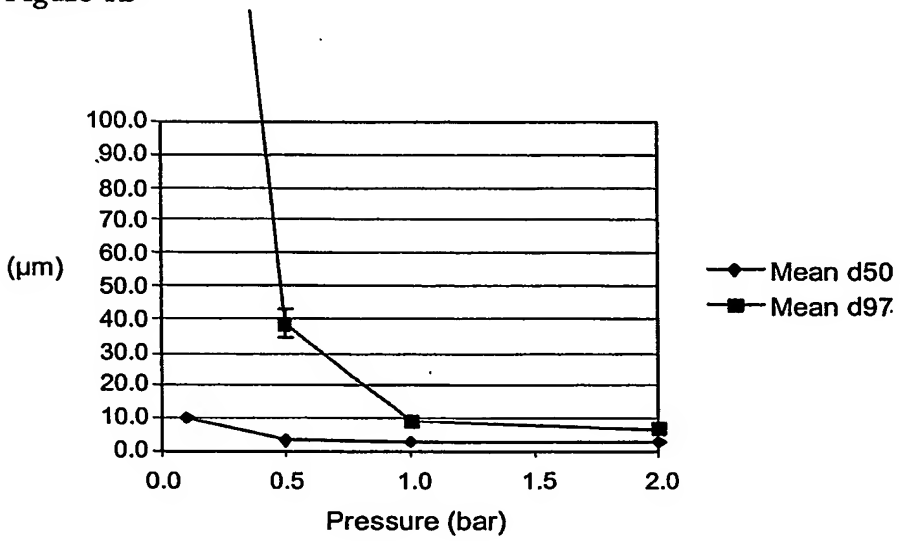


Figure 2A

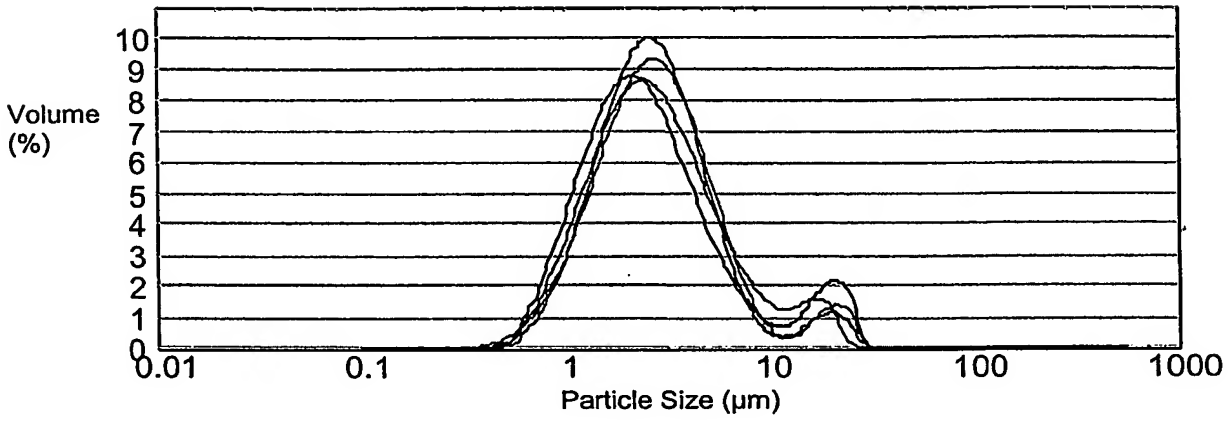


Figure 2B

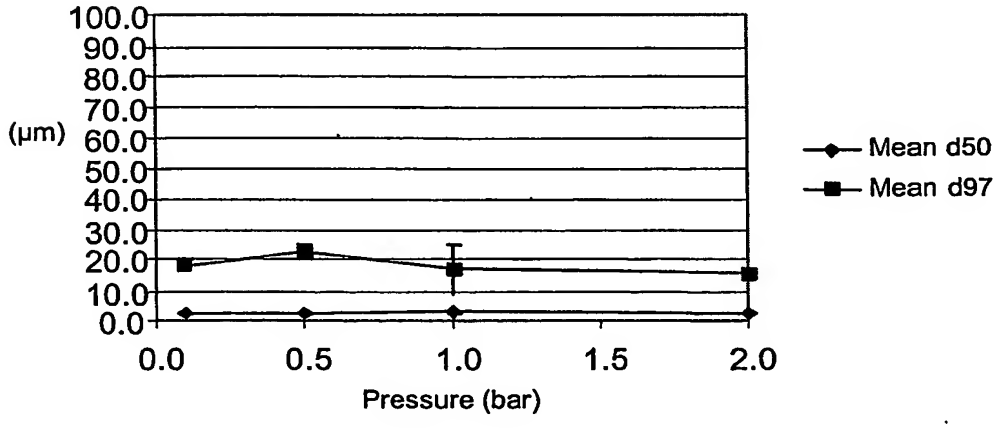


Figure 3A

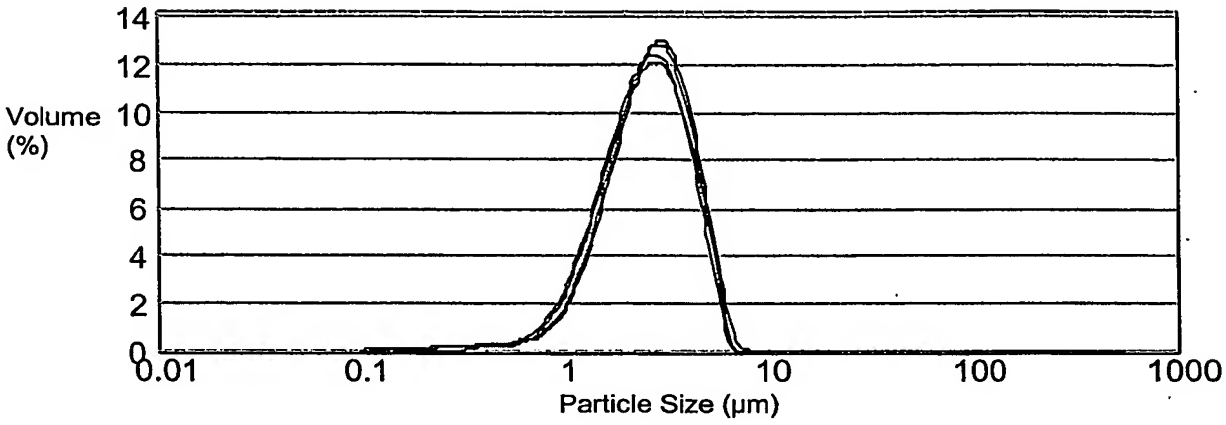


Figure 3B

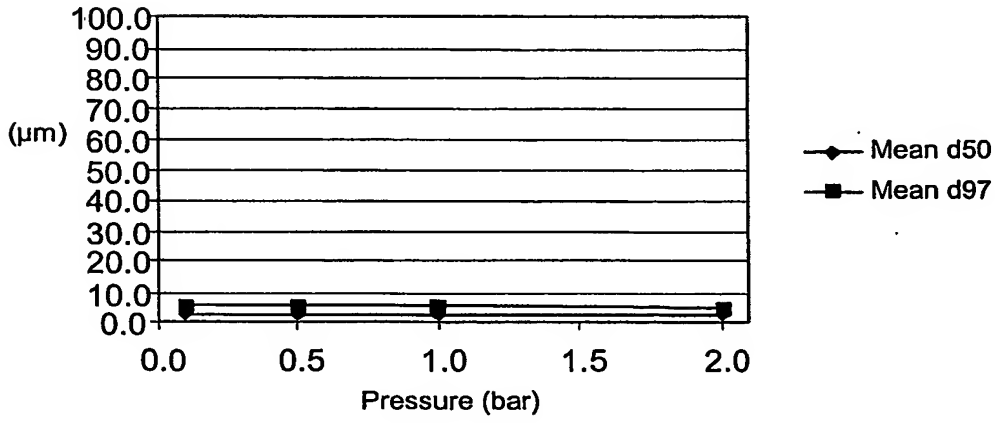


Figure 4A

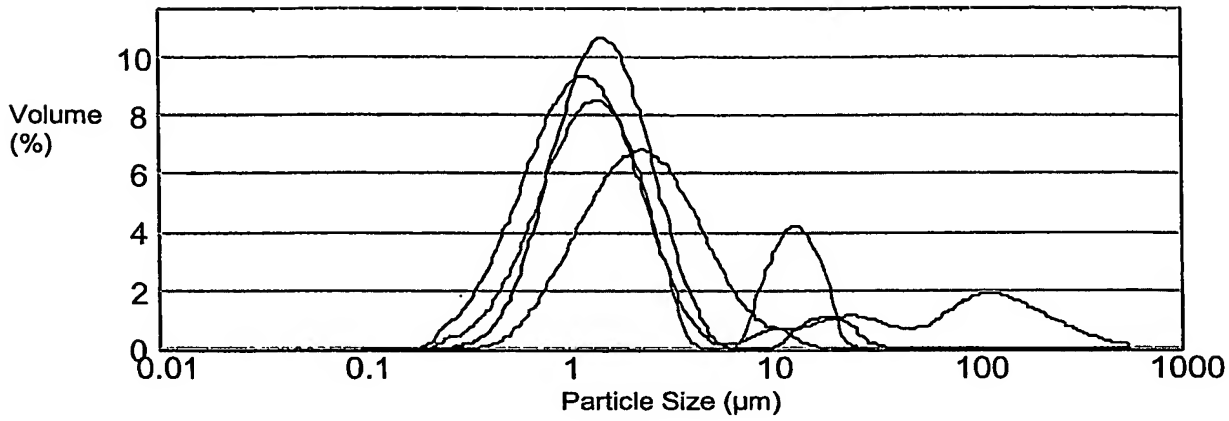


Figure 4B

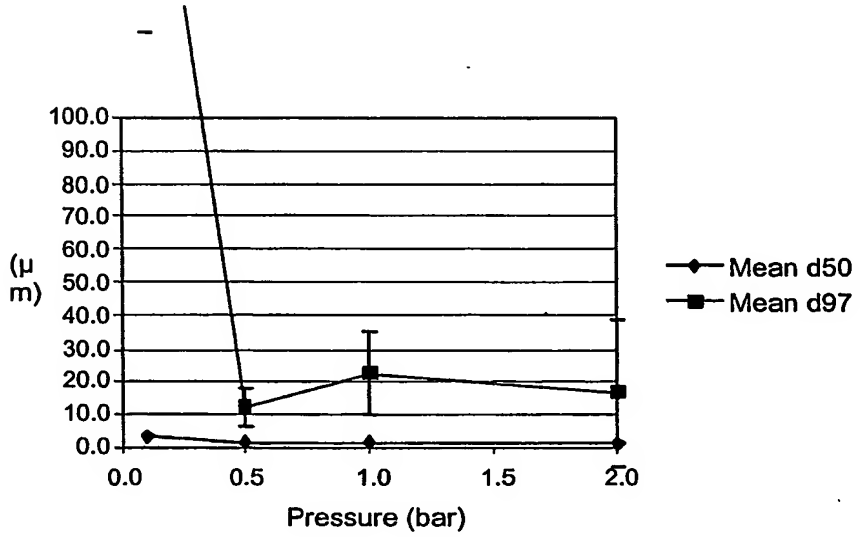


Figure 5A

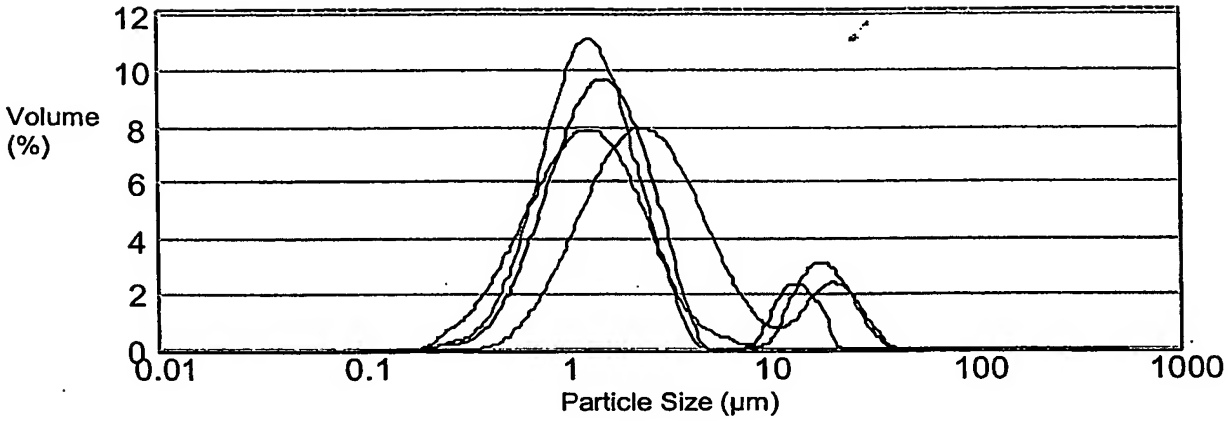


Figure 5B

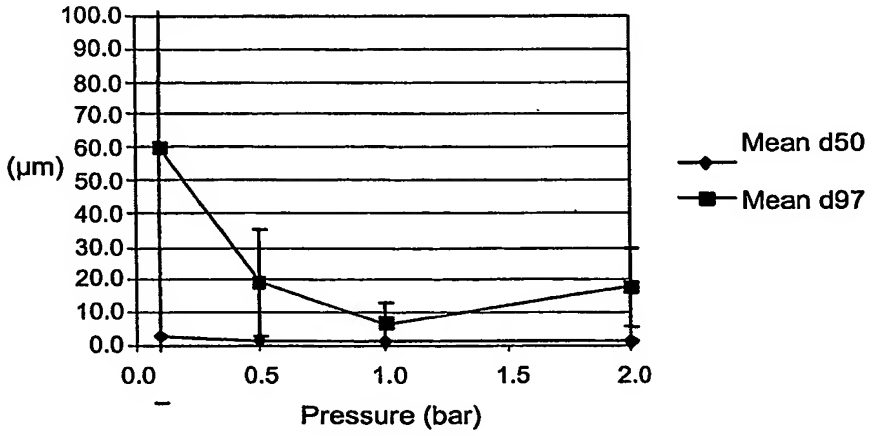


Figure 6A

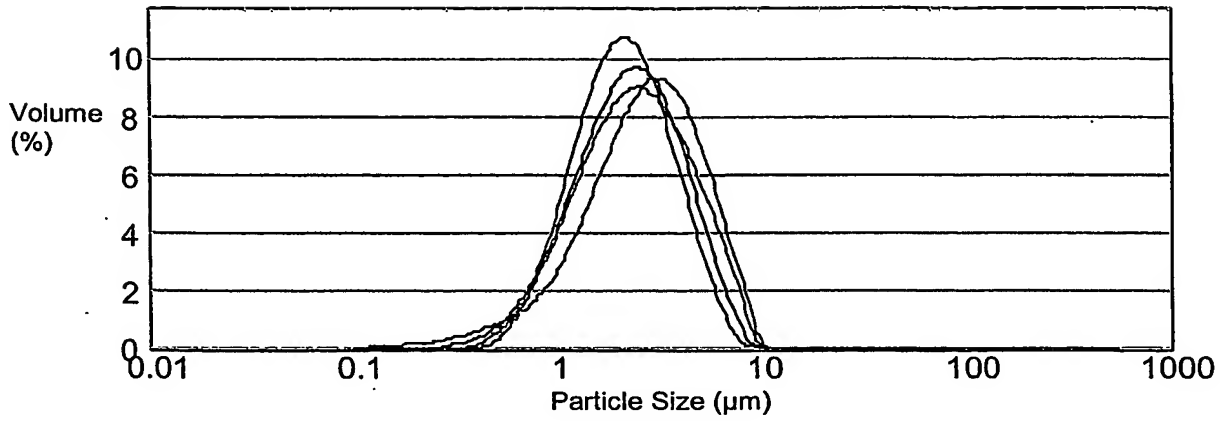


Figure 6B

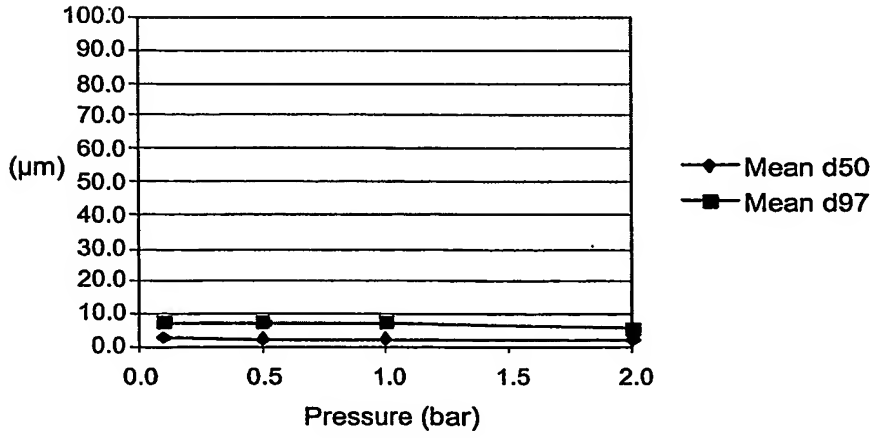


Figure 7A

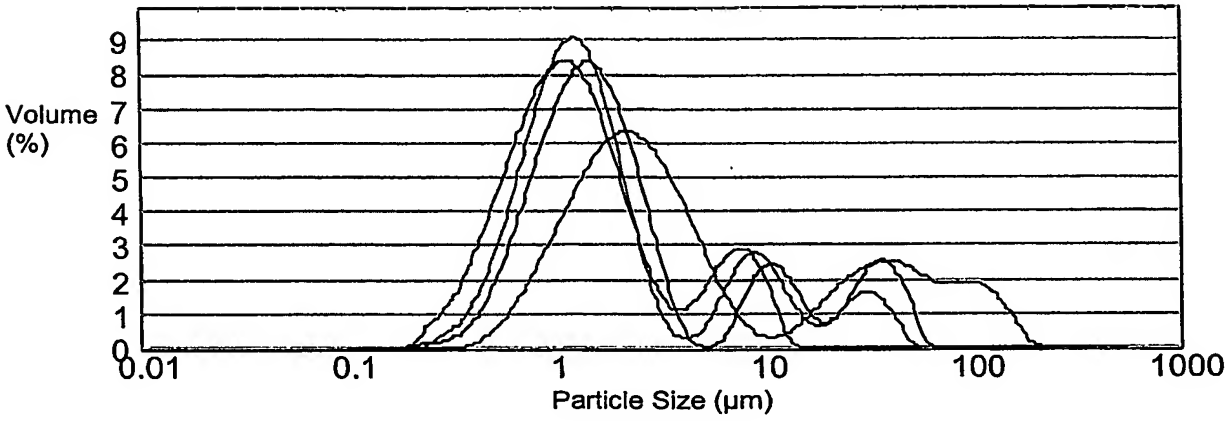


Figure 7B